

Remarks

Reconsideration of this Application is respectfully requested. Upon entry of the foregoing amendment, claims 1, 3-8, 14-19, 36-37, 59, 61-64, and 70-75 are active in the application, with claims 1 and 59 being the independent claims.

The claims from Restriction Requirement Groups III (claims 20-35 and 38-54) and IV (claims 55-58 and 76-78) have been canceled.

The claims from Restriction Requirement Group II, (claims 9-12 and 65-68) are withdrawn. Claims 1, 3-6, 16, 36-37, 59-61, 72 and 75 are linking claims for Groups I and II.

Applicants reserve the right to file one or more continuation or divisional applications directed to the canceled subject matter.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

The Objections to the Claims

Claims 14, 15, 63, 70 and 71 are objected to as depending from a canceled claim. The claims have been amended to depend as interpreted by the Examiner. Applicants thank the Examiner for reviewing the claims in this manner. Accordingly the claim objections can be withdrawn.

The Rejection Under 35 U.S.C. § 112, first paragraph (written description)

At office action page 3, claims 1 and 59 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner asserts that the specification does not describe the complete structure of a representative number of species of the large genus of integrin antagonists, and further that such antagonists are not described by other identifying characteristics, specific features or functional attributes that would distinguish different members of the claimed genus. The Examiner asserts that group of integrin antagonists that are listed in the specification do not share a common structure and that therefore Applicants are not entitled to recite the genus of all integrin antagonists in the claims.

Applicants respectfully disagree with the analysis and respectfully assert that the Office has not established a *prima facie* case of lack of written description. The specification describes a sufficient number of representative examples of integrin antagonists, sufficient to support a genus claim to the use of such antagonists. The integrin antagonists do not require a single common structure to be useful in the claims. Rather it is only that the compound have the biological activity of being an integrin antagonist. That the compound is useful as an integrin antagonist is a sufficient identifying characteristic and functional attribute to make such compound useful in the claimed invention. Applicants respectfully assert that the skilled artisan who read Applicants specification would clearly realize that Applicants were in possession of the claimed genus.

However, in the interests of advancing prosecution, Applicants have amended claims 1 and 59 to recite specific antagonists, support for which can be found on page 19 of the specification. Accordingly, this rejection can be withdrawn.

The Rejection Under 35 U.S.C. § 112, first paragraph (enablement)

At office action page 6, claims 1 and 59 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Examiner asserts that the specification does not provide sufficient guidance to practice the claimed method with any integrin antagonist and an artisan of skill would have required extensive experimentation to practice the claimed invention commensurate with the scope of the claims.

Applicants respectfully disagree with this analysis and respectfully assert that the Office has not established a *prima facie* case of lack of enablement. The teachings of the specification are sufficient to support the use of integrin antagonists in the claimed methods. However, in the interests of advancing prosecution, Applicants have amended claims 1 and 59 to recite specific antagonists, as listed at pages 13 and 14 of the office action. Accordingly, this rejection can be withdrawn.

The Rejection Under 35 U.S.C. § 102(b)

At office action page 14, claims 1, 3, 4, 7, 8, 16-18, 37, 59, 63, 64 and 72-74 are rejected under 35 U.S.C. § 102(b) as being anticipated by Harris-White *et al.*, *The Journal of Neurosci.* 18: 10366-10374 (1998) (hereinafter "Harris-White") as evidenced

by Sabo *et al. Neuroscience Lett. 184: 25-28 (1995)*. Applicants respectfully traverse this rejection.

The Examiner asserts that the art teaches that amyloid- β is an integrin antagonist. Applicants have amended independent claims 1 and 59 to refer to integrin antagonists that do not include amyloid- β . Therefore, this rejection is overcome and may be withdrawn.

The First Rejection Under 35 U.S.C. § 103(a)

At office action page 17, claims 1, 5, 6, 36, 59, 61 and 62 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Harris-White as evidenced by Sabo in view of Matter *et al., J. Cell Biology 141:1019-1030 (1998)* (hereinafter "Matter"). Applicants respectfully traverse this rejection.

The Examiner asserts that it would have been obvious to an artisan of ordinary skill at the time of the invention to modify the hippocampal brain slice method of Harris-White by adding a substance prior to exposure to an integrin antagonist (i.e. amyloid- β) and to use the modified method to determine whether the substance is capable of inhibiting amyloid- β deposition as taught by Matter with a reasonable expectation of success. Applicants respectfully disagree.

Applicants have amended independent claims 1 and 59 to refer to specific integrin antagonists. Matter does not cure the deficiencies of Harris-White. The Examiner's analysis is clouded by hindsight. Harris-White examines the effect of transforming growth factor- β on the deposition or neurotoxicity of amyloid- β in a hippocampal slice culture. The Examiner states that TGF- β is considered to be the

"substance" and "amyloid- β " is considered to be the antagonist. Matter is relied on as teaching integrin $\alpha 5$ as the "substance" and amyloid- β as the "integrin antagonist."

Harris-White, even in combination with Matter, does not teach or suggest exposing brain cells to an integrin antagonist as recited in the amended claims (function blocking anti- $\alpha 5$ subunit integrin antibody, function blocking anti- $\beta 1$ subunit integrin antibody, RGDS peptide, GRGDS peptide, GRGDSP peptide, GRGDTP peptide, echistatin and β -amyloid), and determining the effect of a substance on the ability of the antagonist to have its effect on the sequestration, uptake or accumulation of amyloid as recited in the claimed methods. Accordingly, *prima facie* obviousness is not established and this rejection may be withdrawn.

The Second Rejection Under 35 U.S.C. § 103(a)

At office action page 20, claims 1, 14, 15, 59, 70 and 71 under 35 U.S.C. § 103(a) as being unpatentable over Harris-White as evidenced by Sabo in view of Matter. Applicants respectfully traverse this rejection.

Harris-White is relied on as above. Matter is relied on as teaching a method in which DNA sequences encoding integrin $\alpha 5$ are the "substance" and amyloid- β , anti-integrin $\alpha 5$ antibody and GRGDSP peptides are the "integrin antagonists." Applicants respectfully disagree.

Matter did not determine whether DNA encoding integrin $\alpha 5$ ("the substance" according to the examiner's analysis) had an effect on any of amyloid- β 's, anti-integrin $\alpha 5$ antibody's or the GRGDSP peptide's (the antagonist's) ability to induced sequestration, uptake or accumulation of amyloid. Rather, Matter does the reverse. For example, in Figure 5, the reduction of the A β 1-40 matrix deposition in the $\alpha 5\beta 1$ -

expressing cultures was shown to be reversed by the "antagonist," the anti- $\alpha 5$ antibody. So it is not the "substance" which was evaluated, but rather the integrin antagonist.

Matter does not cure the deficiencies of Harris-White. Accordingly, *prima facie* obviousness is not established and this rejection may be withdrawn.

The Third Rejection Under 35 U.S.C. § 103(a)

At office action page 23, claims 1, 19, 59 and 75 under 35 U.S.C. 103(a) as being unpatentable over Harris-White as evidenced by Sabo, in view of Haß (Hass) *et al.*, *J. Biol. Chem.* 273:13892-13897 (1998) (hereinafter "Hass"). Harris-White is discussed above. Haas is relied upon as disclosing protein-protein interactions between amyloid- β precursor protein APP and apoE2, apoE3 and apoE4 and as recognizing that the apoE4 isoform is associated with development of Alzheimer's disease and is considered a susceptibility factor for Alzheimer's disease. Applicants respectfully traverse this rejection.

Applicants have amended independent claims 1 and 59 to refer to specific integrin antagonists. Harris-White is discussed above. Hass does not cure the deficiencies of Harris-White. Accordingly, *prima facie* obviousness is not established and this rejection may be withdrawn.

Conclusion

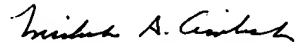
All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the

outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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